EXHIBIT F

CONTROVERSIES IN CARDIOVASCULAR MEDICINE

Drug-Eluting Stents
The Price Is Not Right

Mark J. Eisenberg, MD, MPH

"Does it make economic sense to completely abandon a therapy that works well for 85% to 90% of the population for a new therapy costing four times as much to treat a transient health condition with no impact on either death or myocardial infarction?"

J.M. Brophy and L.J. Erickson[1]

Since Andreas Gruntzig performed the first percutaneous coronary intervention (PCI) in 1977,[2] the cost-effectiveness of this procedure has engendered major controversy. Debates have erupted over the clinical value and cost-effectiveness of each new device or therapy that has become available. Controversies have arisen regarding the cost of atherectomy, bare metal stents (BMS), brachytherapy, distal protection devices, glycoprotein IIb/IIIa inhibitors, and intravascular ultrasound.[3–6] Drug-eluting stents (DES) are the most recent devices to have their cost scrutinized.[7–12]

Response by Ryan and Cohen p 1754

Clinical Effectiveness and DES Penetration

Balloon angioplasty is associated with restenosis rates of 30% to 40%, whereas PCI with BMS is associated with rates of 20% to 30%,[13,14] and PCI with DES is associated with rates in the single digits.[15,16] My colleagues and I pooled the results of 11 DES trials involving >5000 patients using a hierarchical Bayesian random-effects model.[17] We found that, compared with BMS, DES reduce angiographic restenosis from 29.3% to 8.9% (Table 1 and Figure 1). There was no difference between DES and BMS in terms of mortality (0.9% versus 0.9%, respectively) or myocardial infarction (2.7% versus 2.9%, respectively). There was a suggestion that restenosis was less with sirolimus-eluting stents (SES) compared with polymeric paclitaxel-eluting stents (PES) (6.2% for SES versus 36.9% for BMS; 7.1% for PES versus 23.5% for BMS), a finding that was subsequently identified in another meta-analysis.[18]

The interventional community quickly embraced the results of the DES trials. DES use has become nearly ubiquitous in the United States,[19] and its use is becoming widespread outside the United States as well. Rather than reserving this high-cost technology for patients who are at high risk for restenosis, many interventional cardiologists are placing these stents in all patients, including those whose baseline risk of restenosis is low. Before the universal use of DES becomes an entrenched practice, we need to know the answer to the following question: Is the clinical benefit associated with DES substantial enough to justify the use of this high-cost technology in all patients undergoing PCI? Several lines of evidence suggest that DES are currently too expensive to be used in an across-the-board manner in all patients undergoing PCI. These data come from a variety of studies comparing the cost-effectiveness of DES and BMS that have been performed in various countries.

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TABLE 1. Clinical Events and Restenosis Rates in Randomized Clinical Trials Investigating DESs

	Angiographic Restenosis, %		Repeat Revascularization, %*		Myocardial Infarction, %†		Mortality, %		MACE, %	
Trial	DES	BMS	DES	BMS	DES	BMS	DES	BMS	DES	BMS
Sirolimus										
RAVEL	0	26.3	0	22.9	3.3	4.2	1.7	1.7	5.8	29.7
SIRIUS	8.9	36.3	4.1	16.6	2.8	3.2	0.9	0.6	7.1	18.9
C-SIRIUS	2.3	51.1	4.0	18.0	2.0	4.0	0	0	4.0	18.0
E-SIRIUS	5.9	42.3	4.0	20.9	4.6	2.3	1.1	0.6	8.0	22.6
Pooled	6.2	36.9	3.5	18.5	3.2	3.2	1.0	0.7	6.8	21.0
Paclitaxel, polymeric										
TAXUS I	0	10.3	0	10.0	0	0	0	0	3.2	10.0
TAXUS II	7.1	21.9	4.2	14.4	3.1	5.3	0‡	0.8‡	10.4	21.7
TAXUS IV	7.9	26.6	3.0	11.3	3.5	3.7	1.4‡	1.1‡	8.5§	15.1§
Pooled	7.1	23.5	3.3	12.2	3.3	4.0	0.9	1.0	8.7	16.7
Paclitaxel, nonpolymeric										
ASPECT	8.0	27.3	6.8	3.4	2.6	1.7	0.9	0	8.5	5.2
ELUTES	13.1	21.6	7.2	15.8	1.3	0	0.7	0	9.9	18.4
DELIVER	16.7	22.4	5.2	6.8	1.4	1.0	1.0	1.0	6.6¶	8.6¶
PATENCY	38.1	35.3	12.5	19.2	0	0	0	3.8	12.5	23.1
Pooled	14.8	23.8	6.0	7.6	1.5	0.9	0.9	0.9	7.7	9.5
Sirolimus and paclitaxel pooled	8.9	29.3	4.2	13.2	2.7	2.9	0.9	0.9	7.8	8.9

MACE indicates major adverse cardiac events; RAVEL, Randomized study with the sirolimus-eluting Bx Velocity balloon-expandable stent (Cypher); ASPECT, ASian Paclitaxel-Eluting stent Clinical Trial; ELUTES, European evaLUation of pacliTaxel Eluting Stent; and PATENCY, PAclitaxel-eluting sTENt for CYtostatic prevention of restenosis.

*Revascularization by repeat PCI or coronary artery bypass surgery of the index lesion, including for stent thrombosis.

†Both Q wave and non–Q wave.

‡Cardiac deaths only.

§These are the correct rates; there was an error in the original article.

¶The MACE rate in this study included only cardiac deaths.

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Cost-Effectiveness of DES Versus BMS

A PubMed search for studies comparing the cost-effectiveness of DES versus BMS identified 7 studies from North America (Table 2)[20–26] and 6 studies from Australia and Europe (Table 3).[27–32] Only studies that reported cost per quality-adjusted life-year (QALY) gained or cost per repeat revascularization avoided were included. Cost per QALY gained is the primary outcome measure of most cost-effectiveness analyses. Using this measure, we can directly compare the cost-effectiveness of different healthcare interventions (Table 4).[33] In the United States, an intervention associated with a cost per QALY gained of <$50 000 is considered to be cost-effective; one associated with a cost per QALY gained of $50 000 to $100 000 is in the "gray area"; and one associated with a cost per QALY gained of >$100 000 is considered unattractive.[34] Cost per repeat revascularization avoided is the other measure that is commonly used in DES cost-effectiveness studies. This disease-specific measure allows us to examine whether the incremental cost of DES above that of BMS is offset by the cost savings brought about by a reduction in the need for subsequent revascularization procedures. In the United States, a cost per revascularization avoided <$10 000 is thought to be cost-effective.[20,21]

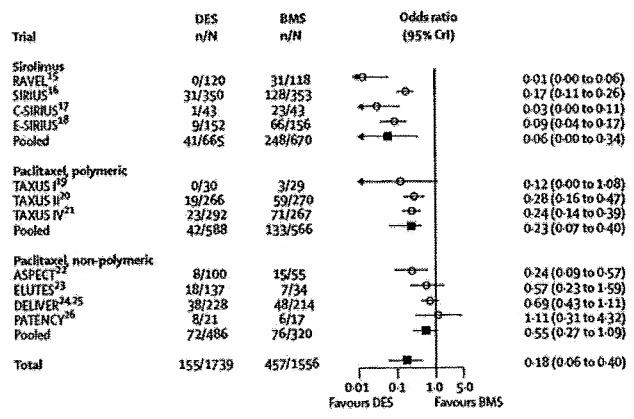

Figure 1. Forest plot comparing rates of angiographic restenosis for DES and BMS. Reproduced from Babapulle et al[17] with permission from Elsevier. Copyright 2004.

Cost-Effectiveness Studies of DES in the United States

At the time of this writing, only 2 traditional cost-effectiveness studies examining DES in the context of the

TABLE 2. Cost-Effectiveness Studies of DES in North America

Location and Author	Source of Efficacy Data	Source of Cost Data	Patient Group, n	Assumptions				Outcomes at 12 Months	
				Mean Stents, n (type)	Revascularization Rate, DES vs BMS, %	Cost of DES vs Cost of BMS	Cost of PCI vs Cost of CABG	Cost per QALY Gained	Cost per Revascularization Avoided
United States (costs in $US)									
Greenberg et al[20]	BMS data, RAVEL, SIRIUS	Multicenter trials	Single vessel, 6000	1.3 (SES)	3.8 vs 14.0	2700 vs 700	NR vs 25 000	NR	7000*
Cohen et al[21]	SIRIUS	Hospital and Medicare rates	Complex†, 1058	1.4 (SES)	16.3 vs 35.4	2900 vs 900	4395 (7251)‡ vs NR	27 540	1650
Canada (costs in $CAN)									
Bowen et al[22]	CCN CARDIACCESS	NR	No DM, no MI, 4796	1.5 (Both)	9.4 vs 10.7	1899 vs 600	≈7050 vs 18 799	2 221 692	95 383
			No DM, post-MI, 1432	1.5 (Both)	10.0 vs 13.1	1899 vs 600	≈7050 vs 18 799	1 688 786	69 696
			DM, no MI, 1377	1.5 (Both)	11.1 vs 13.5	1899 vs 600	≈7050 vs 18 799	1 132 426	49 333
			DM, post-MI, 348	1.5 (Both)	12.1 vs 16.9	1899 vs 600	≈7050 vs 18 799	438 415	17 711
Shrive et al[23]	APPROACH	APPROACH, Alberta Health	Complex†, 7334	1.4 (SES)	NR	2900 vs 500	15 569 vs 32 009	58 721	NR
Mittmann et al[24]	Meta-analysis	RCTs, Ontario Medicare, personal communication	Complex†, 2447	1.5 (PES)	3.3 vs 12.2	2400 vs 608	9761 vs 19 617	NR	26 562
			Complex†, 1748	1.5 (SES)	3.5 vs 18.5	2400 vs 608	9761 vs 19 617	NR	12 527
Brophy et al[1,25]	Meta-analysis[17]	Hospital costs, Quebec Medicare	Complex†, 1400	1.7 (NR)	3.3 vs 12.8	2600 vs 700	4507 vs 15 025	NR	23 067§
Rinfret et al[26]	C-SIRIUS	CHUM, RAMQ	Single vessel, 100	1.5 (SES)	4.0 vs 22.0	2700 vs 700	4006 vs 14 402	NR	11 275

CABG indicates coronary artery bypass grafting; QALY, quality-adjusted life-years; NR, not reported; CCN, Cardiac Care Network of Ontario; CARDIACCESS, patient registry of the CCN; DM, diabetes mellitus; MI, myocardial infarction; APPROACH, Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease; RCTs, Randomized Controlled Trials; CHUM, Centre Hospitalier de l'Université de Montréal; and RAMQ, Régie de l'assurance maladie du Québec.

*After follow-up of 2 years.

†Complex includes all patients, including those with diabetes, long lesions, small vessels, and multivessel disease.

‡Cost of BMS PCI (cost of SES PCI) including stent price.

§After follow-up of 9 months.

United States have been published; both are from the same group at the Harvard Clinical Research Institute (Table 2).[20,21] Despite these surprisingly limited cost-effectiveness data, DES are being used in the vast majority of PCI procedures now being performed in the United States.[19]

Greenberg et al[20] published a review of the economic impact of restenosis and DES. Embedded within the review was a decision-analytic model examining DES cost-effectiveness. The model used outcome and resource use data from >6000 "real-world" patients undergoing single-vessel PCI procedures.[35–37] Costs were based on pooled data from several clinical trials involving >3000 patients. The model used the following assumptions: (1) a BMS repeat revascularization rate of 14%, (2) an 80% reduction in repeat revascularization rates with DES, (3) an incremental cost of $2000 per DES, and (4) a mean use of 1.3 stents per PCI. Over a 2-year follow-up, this model indicated that overall medical care costs are approximately $900 per patient higher with DES than with BMS, with an incremental cost-effectiveness ratio of approximately $7000 per repeat revascularization avoided. Sensitivity analyses suggested that treatment with DES is cost saving for patients with a BMS repeat revascularization rate >20% and cost-effective (<$10 000 per repeat revascularization avoided) for patients with a BMS repeat revascularization rate >12% (Figure 2). The authors concluded that, compared with BMS, DES are cost saving for only a modest proportion of the current PCI population in the United States. However, they did suggest that DES are economically attractive for virtually all diabetic patients and for nondiabetic patients with small vessels and long lesions. Greenberg et al did not report a cost per QALY gained, but they concluded that the cost-effectiveness of DES is dependent on the target population undergoing PCI and the alternative therapy that might be used (ie, medical therapy, BMS, or coronary artery bypass grafting.

Cohen et al[21] reported an economic analysis of the SIRIUS trial.[2] Clinical outcomes, resource use, and costs were prospectively collected for 1058 patients who received either an SES or a BMS over a 1-year period. Initial hospital costs were increased by $2881 per patient with DES. During the 1-year follow-up, use of DES versus BMS was associated with reductions in the rates of repeat PCI (12.4% versus 26.9%, respectively) and bypass surgery (1.3% versus 3.0%, respectively). Although follow-up costs were reduced by $2571 per patient with DES, aggregate 1-year costs were still $309 per patient higher. The incremental cost-effectiveness ratios for DES were $27 540 per QALY gained and $1650 per repeat revascularization avoided. The authors concluded that, al-

TABLE 3. Cost-Effectiveness Studies of DES in Australia and Europe

Location and Author	Source of Efficacy Data	Source of Cost Data	Patient Group, n	Assumptions: Mean Stents, n	Assumptions: Revascularization. Rate, DES vs BMS, %	Assumptions: Cost of DES vs Cost of BMS	Assumptions: Cost of PCI vs Cost of CABG	Outcomes at 12 Months: Cost per QALY Gained	Outcomes at 12 Months: Cost per Revascularization Avoided
Australia (cost in $AUS)									
Lord et al[27]	TAXUS, SIRIUS, RAVEL	National Hospital Cost Data	Complex*, 1748	1.5 (SES)	4.0 vs 20.5	2000 vs 850	NR	46 829	3746
			Complex*, 1642	1.5 (PES)	4.5 vs 14.6	2000 vs 850	NR	76 467	6117
Ward[28]	Patient registry	Department of Health	Complex*, 490	1.1 (NR)	0 vs 5	Δ1700	5186 vs 18 496	NR	28 349
Sweden (cost in SEK)									
Ekman et al[29]	TAXUS IV	Hospital Price Lists	Complex*, 13 200	1.4 (PES)	4.5 vs 15.9	Δ9600	52 300-66 020 vs 134 507	2 350 844	46 801
			High risk†, NR	1.4 (PES)	6 vs 22	Δ9600	52 300–66 020 vs 134 507	381 554	7648
Switzerland (cost in €)									
Kaiser et al[30]	BASKET	TARMED	Complex*, 826	1.4 (Both)	7.2 vs 12.1	1935–2380‡ vs 1300-1260‡	3095 vs 7095	73 283‡	18 311§
United Kingdom (cost in GBP)									
Bagust et al[31]	CTC, RAVEL, SIRIUS	CTC and NHS Costs	Elective PCI, 1951	1.9 (SES)	7.5 vs 24.9	Δ500	3190 vs 7750	NR	51 600–238 900
			Nonelective PCI, 933	1.7 (SES)	NR	Δ500	4179 vs 7750	NR	−23 700–133 600
NICE[32]	TAXUS II, RAVEL	NR	Single-vessel disease, NR	1.0 (NR)	2.7 vs 12.7	900 vs 380	2156 vs 8368	24 325	1080

CABG indicates coronary artery bypass grafting; QALY, quality-adjusted life-years; NR, not reported; RAVEL, Randomized study with the sirolimus-eluting Bx Velocity balloon-expandable stent (Cypher); BASKET, Basel Stent Kosten Effektivitäts Trial; TARMED, Swiss Medical tariff; CTC, cardiothoracic center; NHS, National Health Service; and NICE, National Institute for Clinical Excellence.

*Complex includes all patients, including those with diabetes, long lesions, small vessels, and multivessel disease.

†High risk includes patients with diabetes, small vessels, and/or long lesions.

‡Prices vary depending on the type of DES or BMS used.

§After follow-up of 6 months.

though the use of SES was not cost saving compared with BMS, for patients undergoing PCI of complex coronary lesions, the use of DES appeared to be reasonably cost-effective within the context of the United States healthcare system.

These 2 studies examining the cost-effectiveness of DES in the context of the United States came to similar conclusions. Both studies suggested that DES are cost-effective in high-risk patients with respect to repeat revascularizations avoided. In addition, although the study by Greenberg et al[20] did not report a cost per QALY gained, the figure reported by Cohen et al[21] falls within the range that is generally accepted as being cost-effective in the United States (<$50 000 per QALY gained) (Table 4). However, the conclusions drawn from these 2 studies must be tempered in view of the assumptions and methodologies used.

Greenberg et al[20] assumed that all patients underwent single-vessel PCI with a mean use of 1.3 DES per procedure. In contrast, other cost-effectiveness studies assumed a mean use of 1.5 DES per PCI; some have even used 1.7 or 1.9 (Tables 2 and 3). Minimizing the number of DES used per PCI minimizes the estimated cost per repeat revascularization avoided. In addition, because DES allow us to treat more complex lesions than were treated previously, it is likely that future PCI procedures will use more rather than fewer stents per case.

Cohen et al[21] performed a textbook-perfect cost-effectiveness study as part of the SIRIUS trial. However, the results of this study were affected by the use of protocol-mandated angiography. Most of the DES trials, including the SIRIUS trial, used protocol-mandated follow-up angiography at 6 to 9 months with subsequent clinical follow-up several months later. Because follow-up angiography was performed in all patients, many cases of angiographic restenosis were identified in patients who were asymptomatic. If restenosis was identified at the time of the protocol-mandated angiography, repeat PCI was frequently performed—often called the oculostenotic reflex. These asymptomatic patients who had angiographic but not clinical restenosis were then identified as achieving one of the predefined end points of the trial: need for repeat revascularization. The effect of protocol-mandated angiography can be seen in the Kaplan-Meier survival curves for the RAndomized study with the sirolimus-eluting Bx VELocity balloon-expandable stent (Cypher; RAVEL) trial (Figure 3).[38] At the time of the mandated

TABLE 4. Cost-Effectiveness and Use of Selected Interventions in the Medicare Population*

Intervention	Cost-Effectiveness†	Implementation
Influenza vaccine	Cost saving	40%–70%
Pneumococcal vaccine	Cost saving	55%–65%
β-Blockers after myocardial infarction	<10 000†	85%
Mammographic screening	10 000–25 000†	50%–70%
Colon-cancer screening	10 000–25 000†	20%–40%
Osteoporosis screening	10 000–25 000†	35%
Management of antidepressant medication	Cost saving up to 30 000†	40%–55%
Hypertension medication (diastolic blood pressure >105 mm Hg)	10 000–60 000†	35%
Cholesterol management, as secondary prevention	10 000–50 000†	30%
Implantable cardioverter-defibrillator	30 000–85 000†	100 000 cases/y
Dialysis in end-stage renal disease	50 000–100 000†	90%
Lung-volume–reduction surgery	100 000–300 000†	10 000–20 000 cases/y
Left ventricular assist devices	500 000–1.4 million†	5000–100 000 cases/y
PET in Alzheimer's disease	Dominated‡	50 000 cases/y

PET indicates positron-emission tomography.

*Ranges rather than point estimates are provided because the actual cost-effectiveness will vary according to the target populations and the strategies used.

†Calculated as cost/QALY. The calculation was based on 2002 dollars.

‡With the use of this intervention, benefits are lower and costs are higher than with the use of the standard workup.

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angiographic follow-up, there was a sharp rise in the identification of restenosis and occurrence of repeat revascularization procedures. Repeat revascularization in the BMS group jumped from 6% before angiography to >20% after angiography. Similar increases were seen in other DES trials that used protocol-mandated angiography (Table 5).[28,39–41] Although Cohen et al tried to account for the use of protocol-mandated angiography in their analysis, they were overly optimistic in both the clinical effectiveness data that they used in their cost analysis and the subsequent DES cost-effectiveness that they reported.

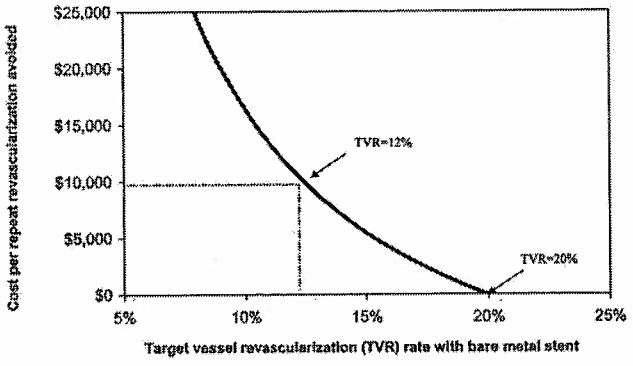

Figure 2. Relationship between the rate of target vessel revascularization with BMS implantation and the incremental cost-effectiveness of DES implantation for patients undergoing single-vessel PCI. Reproduced from Greenberg et al[20] with permission from the American College of Cardiology Foundation. Copyright 2004.

Cost-Effectiveness Studies of DES Outside the United States

In contrast to the 2 published studies from the United States, 5 studies from Canada suggest that across-the-board use of DES in all PCI patients is not cost-effective. Although the Canadian dollar is worth ≈90 cents American at the time of this writing, the thresholds considered to be cost-effective in Canada are somewhat different than those in the United States. The reason for this is that the costs of repeat PCI and

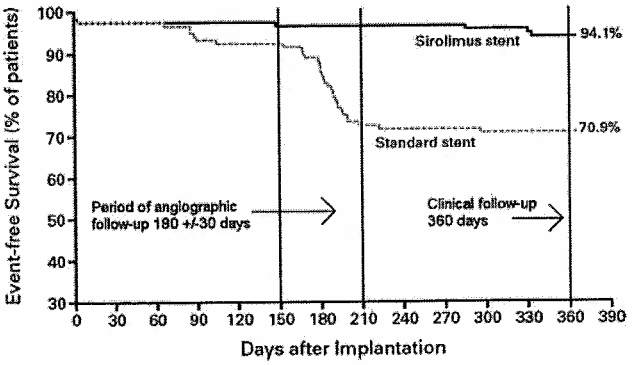

Figure 3. Kaplan-Meier estimates of survival free of myocardial infarction and repeated revascularization among patients who received SES and those who received BMS in the RAVEL trial. The percent of event-free patients in the BMS group decreased rapidly during the period of angiographic follow-up. This decrease was due to an increase in restenosis and subsequent target lesion revascularizations identified by the angiographic follow-up. Adapted and reproduced from Morice et al with permission from the Massachusetts Medical Society. Copyright 2002.

TABLE 5. Target Lesion Revascularization Rates With BMS in DES Trials Before and After Protocol-Mandated Angiography

Trial	Revascularization Rate, %	
	Before Protocol-Mandated Angiography	After Protocol-Mandated Angiography
RAVEL	6	23
SIRIUS	7	17
E-SIRIUS	11	21
TAXUS II	5	15

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coronary artery bypass grafting are much less in Canada.[42] Cost-effectiveness thresholds in Canada are <Can $50 000 per QALY gained and <Can $12 551 per repeat revascularization avoided.[26]

Bowen et al[22] performed a cost-effectiveness analysis of DES for the Ontario Ministry of Health and Long-Term Care. These investigators found that DES were associated with an exceedingly high cost per QALY gained: Can $438 415 to Can $2 221 692, ratios that clearly place this technology in the non–cost-effective range. In addition, the cost per revascularization avoided was also prohibitive: from Can $17 711 for patients with a recent myocardial infarction and diabetes to Can $95 383 for patients without a myocardial infarction or diabetes.

Shrive et al[23] performed a cost-effectiveness analysis of SES on behalf of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) investigators. They found that SES use was associated with a cost per QALY gained of Can $58 721 and that SES use was more cost-effective in patients with diabetes and in those >75 years of age (Can $44 135 and Can $40 129 per QALY gained, respectively). For patients <65 years of age and those without diabetes, SES use was substantially less cost-effective (Can $72 464 and Can $63 383 per QALY gained, respectively).

Mittmann et al[24] performed a cost-effectiveness analysis of DES for the Canadian Coordinating Office for Health Technology Assessment. The investigators found that PES use was associated with a cost per revascularization avoided of Can $26 562 to Can $29 048, whereas SES use was associated with a cost of Can $12 527 to Can $16 600. The investigators did not calculate costs per QALY gained. However, they did examine the impact of DES use on the annual Canadian healthcare budget. They found that extending DES use from the 40% of patients at highest risk for restenosis to 100% of patients undergoing PCI would lead to a >3-fold increase in DES costs but only a 1.5-fold reduction in repeat revascularization procedures.

Brophy and Erickson[25] performed a cost-effectiveness analysis of DES for the Quebec Agency for the Evaluation of Technology and Health Interventions. The investigators calculated that cost per revascularization avoided would increase from Can $7000 at 20% DES penetration to Can $23 067 at 100% DES penetration. The investigators also calculated the price at which DES use would be cost neutral assuming different DES penetration rates. With a 20% use in patients at highest risk, the break-even cost for DES would be Can $1663; at 60%, it would be Can $1266; and at 100%, it would be Can $1161.

Rinfret et al[26] investigated the cost-effectiveness of SES versus BMS in high-risk patients with single long de novo lesions in small coronary arteries. These investigations found that BMS use versus balloon angioplasty is associated with a cost per repeat revascularization avoided of Can $12 551 and that SES versus BMS use was associated with a cost per repeat revascularization avoided of Can $11 275. The investigators concluded that DES are borderline cost-effective in Canada in a high-risk subgroup of patients.

Thus, 5 cost-effectiveness studies from Canada suggest that DES are not an attractive therapy to be used in an across-the-board manner. The authors of each of these studies suggested that, at current prices, DES are too expensive to be cost-effective except in selected groups of high-risk patients.

Authors of DES cost-effectiveness studies in Australia, Sweden, Switzerland, and the United Kingdom all reported results similar to those found in Canada (Table 3). Importantly, the BAsel Stent Kosten Effektivitäts Trial (BASKET) investigators prospectively performed a study in which they examined the cost-effectiveness of DES in a group of patients randomized to DES or BMS.[30] As opposed to most other studies, costs were prospectively collected, and patients did not undergo protocol-mandated follow-up angiography. A total of 826 patients were randomized to SES, PES, or BMS. The aggregate costs at 6 months were higher with DES than with BMS, and higher stent costs were not compensated for by lower follow-up costs (overall 6-month costs were still 905 € higher in the DES group). The incremental cost-effectiveness ratio to avoid 1 major adverse cardiac event was 18 311 €, and the cost per QALY gained was more than 50 000 €. The authors concluded that, in a real-world setting, use of DES should be restricted to patients in high-risk groups. Importantly, BASKET also suggested that DES are associated with a significantly higher rate of thrombotic complications compared with BMS during the 6 months following the cessation of clopidogrel.[43] Therefore, the need for prolonged treatment with clopidogrel will further reduce the cost-effectiveness of DES.

Limitations of DES Cost-Effectiveness Studies

Despite the fact that most studies have not found DES to be cost-effective in an across-the-board manner, many of these studies still painted an overly optimistic picture of the cost-effectiveness of DES. Two limitations of these studies were responsible. First, the true cost of DES procedures was

underestimated; second, the clinical effectiveness of DES was overestimated.

Although the cost of a single DES is reasonably well established, the published studies used a mean number of stents per PCI between 1.0 and 1.9. The assumption of a lower number of stents per PCI leads to a better cost-effectiveness ratio; the assumption of a higher number leads to a worse cost-effectiveness ratio. With the advent of DES, there has been a trend of performing increasingly complex PCI procedures. This trend will likely lead to an even greater number of stents per patient in the future. Thus, previous studies underestimated the true cost of DES procedures, and this led to an overly optimistic view of DES cost-effectiveness.

Previous studies also overestimated the clinical effectiveness of DES. Most of these studies based their calculations on data obtained from previous DES trials. Unfortunately, most of these trials enrolled patients with solitary de novo coronary lesions and used protocol-mandated angiography. These features led to the observations of low restenosis rates in patients receiving DES and high rates of restenosis and repeat revascularization procedures in patients receiving BMS. The use of inflated estimates of clinical effectiveness led to overly optimistic estimates of DES cost-effectiveness. Studies like the BASKET trial that were performed in real-world settings without the use of protocol-mandated angiography found that the clinical benefit of DES is substantially less than that described in randomized controlled trials. Consequently, the cost-effectiveness studies that relied on the early DES trials were overly optimistic in the clinical effectiveness data that they used.

Conclusions From DES Cost-Effectiveness Studies

Despite their limitations, several important conclusions can be derived from the DES cost-effectiveness studies that have been published. First, DES are not cost saving and they are not cost neutral. A substantial amount of money has to be spent to obtain a modest clinical benefit. Second, if DES are used in place of BMS, some but not all of the initial cost is recouped during the follow-up period as a result of a reduced need for repeat revascularization procedures. Third, because DES have no impact on mortality or myocardial infarction rates and because their effect on quality of life is modest, DES are associated with a high cost per QALY gained. Thus, the sole justification for the use of DES is their ability to reduce the need for repeat revascularization procedures. If these procedures are expensive, the incremental cost-effectiveness ratios associated with DES are attractive; if these procedures are inexpensive, the incremental cost-effectiveness ratios are unattractive. Finally, the cost-effectiveness of DES can be markedly enhanced by either decreasing their price or reserving their use for patients who are at high risk for restenosis. At current prices, using DES in an across-the-board manner is not an optimal strategy from a cost-effectiveness point of view.

Other DES Cost Studies

Besides the traditional cost-effectiveness studies detailed above, a number of studies have examined the economics of DES from other perspectives. Several studies examined the decline in DES price required for DES to be cost neutral (the break-even price).[44,45] Several studies examined the impact of DES penetration on hospital budgets,[46,47] and other studies examined the impact of DES on global healthcare budgets.[48–51] The conclusions from these studies can be summarized as follows. First, DES prices have to decline substantially before break-even prices are reached. Second, from both hospital and societal perspectives, across-the-board use of DES leads to substantial increases in budgetary costs that are not recouped by a reduced need for subsequent revascularization procedures.

Competing Healthcare Interventions

Another issue should be considered before deciding on a policy to guide our use of DES. Even in affluent societies, resources available for healthcare interventions are not unlimited.[48] In reality, multiple potential healthcare interventions are in competition for the same resources; consequently, some interventions receive funding while others do not. The best way to determine which interventions will be funded is not by individual studies of cost-effectiveness but instead by directly contrasting the cost-effectiveness ratios of alternative interventions. Many healthcare interventions are associated with a cost per QALY gained in the gray area of $50 000 to $100 000. If we funded each of these interventions, we would quickly deplete the budget of every hospital and every healthcare system. The most efficient, and perhaps the most equitable, way of using our limited healthcare resources is by reimbursing for the most cost-effective interventions. Our budget should first be spent on the most cost-effective intervention, followed by the second most cost-effective intervention, and so on until our resources are spent. In this fashion, the most health benefit is obtained for a given amount of limited resources. The current method of comparing healthcare interventions in isolation leads to inequities. Many high-cost but low-yield interventions are currently available, but other low-cost but high-yield interventions are not. With this perspective in mind, an across-the-board use of DES cannot be justified.

When Is DES Use Cost-Effective?

Although DES are not cost-effective in an across-the-board manner, at current prices, DES may well be cost-effective in several subgroups of high-risk patients. These subgroups include patients at high risk for restenosis (eg, diabetics and those with long lesions and small vessels) (Table 6)[37] and patients who would otherwise undergo coronary artery bypass surgery. Other subgroups in which DES may prove to be

TABLE 6. Predicted Rates of Clinical Restenosis After BMS Implantation as a Function of Lesion Length, Reference Vessel Diameter, and Diabetes

	Lesion Length, mm						
Vessel Diameter (mm)	10	15	20	25	30	35	40
Diabetic patients, %							
2.5	18	21	24	28	33	38	45
3.0	12	14	16	18	21	25	29
3.5	8	9	10	12	14	16	19
4.0	5	6	7	8	9	10	12
Nondiabetic patients, %							
2.5	11	13	15	18	21	24	28
3.0	7	8	10	11	13	15	18
3.5	5	5	6	7	9	10	12
4.0	3	4	4	5	6	6	7

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cost-effective include patients with left main lesions, patients with proximal left anterior descending artery lesions, patients with lesions in saphenous vein grafts, and patients with complex lesions who are at high risk for restenosis. However, at this time, few cost-effectiveness data have been derived directly from these high-risk subgroups. The data that are available are mostly extrapolated rather than directly measured. The cost-effectiveness of DES in these high-risk subgroups should be closely explored before the routine use of DES in these patients becomes entrenched.

Ethical Considerations

If DES are used in an across-the-board manner in all PCI patients, well over half of the patients who receive these stents will not derive any clinical benefit from them. One has to question whether it is ethical to subject large numbers of patients who are at low risk of restenosis to the small but real risk of late thrombosis known to be associated with DES.[52–54] Moreover, the widespread use of DES and the ensuing risk of late thrombosis is creating a new clinical phenomenon: long-term dependence on clopidogrel. With an aging population and with the increased bleeding risks associated with clopidogrel, we may need to temper our enthusiasm regarding DES. One also has to question whether it is ethical to use an extremely high-cost technology in many patients who will not derive any clinical benefit while denying more essential health care to many patients who do not have the financial resources to pay for it. Although framing the issue in this manner may not be popular, policy makers in many countries have decided that using BMS in patients at low risk of restenosis will free up valuable resources that can be used to improve health care in other arenas. With an increasing realization that limited healthcare resources must be used in an optimal manner, a healthy debate about the ethics of using DES at their current prices in an across-the-board manner should be encouraged.

Conclusions

Almost 30 years after Andreas Gruntzig performed the first PCI, the debate about the cost-effectiveness of this procedure still arouses controversy. Interventional cardiology is a constantly changing field, and new devices and therapies are continually being introduced. Some of these devices and therapies find a permanent place; others are eventually discarded. After the initial cost-effectiveness debates, virtually all of these devices and therapies drop in price until the cost-effectiveness debates are scarcely remembered. I anticipate that a similar scenario will occur with DES. As second- and third-generation DES become available and as new companies enter the market, prices will drop. In addition, improvements in stent design, use of different polymers, and the introduction of cheaper and more effective drugs that can be eluted from stents will lead to an increase in DES effectiveness. As prices drop and clinical effectiveness increases, the cost-effectiveness of DES will improve substantially. Our original question was, Is the clinical benefit associated with DES substantial enough to justify the use of this high-cost technology in all patients undergoing PCI? I think that the cost-effectiveness data that we now have available indicate that DES are currently too expensive to be used in all patients undergoing PCI. However, as their prices drop and as their effectiveness increases, DES will become increasingly attractive from a cost-effectiveness point of view, and their use will likely become a permanent addition to the pantheon of interventional cardiology.

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References

1. Brophy JM, Erickson LJ. Cost-effectiveness of drug-eluting coronary stents in Quebec, Canada. *Int J Technol Assess Health Care*. 2005;21:326–333.
2. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979;301:61–68.
3. Weintraub WS. Economics of coronary stenting and GP IIb/IIIa blockade. *Eur Heart J*. 2001;22:1366–1368.
4. Kandzari DE, Mark DB. Intracoronary brachytherapy: time to sell short? *Circulation*. 2002;106:646–648.
5. Brophy JM, Sleight P. Enthusiasm, reality, and cost-effectiveness analysis. *Heart*. 1998;79:9–11.

6. Vik-Mo H. Intravascular ultrasound improves the quality of coronary interventions, but is it worth the extra time and money invested? *Scand Cardiovasc J*. 2001;35:67–69.
7. Thomas M. Are drug-eluting stents really worth the money? *Heart*. 2006;92:5–7.
8. Brophy JM. The dollars and sense of drug-eluting stents. *Can Med Assoc J*. 2005;172:361–362.
9. Chew DPB. Cost-effectiveness of drug-eluting stents: if only all things were equal: they reduce rates of restenosis but not mortality or infarction–so are they worth it? *Med J Aust*. 2005;182:376–377.
10. Teirstein PS. A chicken in every pot and a drug-eluting stent in every lesion. *Circulation*. 2004;109:1906–1910.
11. Lemos PA, Serruys PW, Sousa JE. Drug-eluting stents: cost versus clinical benefit. *Circulation*. 2003;107:3003–3007.
12. O'Neill WW, Leon MB. Drug-eluting stents: costs versus clinical benefit. *Circulation*. 2003;107:3008–3011.
13. Fischman DL, Leon MB, Baim DS, Fischman DL, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein PS, Fish RD, Colombo A, Brinker J, Moses J, Shaknovich A, Hirshfeld J, Bailey S, Ellis S, Rake R, Goldberg S. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease: Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331:496–501.
14. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy JJ, van den Heuvel P, Delcan J, Morel M. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease: Benestent Study Group. *N Engl J Med*. 1994;331:489–495.
15. Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: part I. *Circulation*. 2002;106:2734–2740.
16. Babapulle MN, Eisenberg MJ. Coated stents for the prevention of restenosis: part II. *Circulation*. 2002;106:2859–2866.
17. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet*. 2004;364:583–591.
18. Kastrati A, Dibra A, Eberle S, Mehilli J, de Lezo JS, Goy JJ, Ulm K, Schomig A. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA*. 2005;294:819–825.
19. Marks DS, Ratko TA, Matuszewski KA, Oinonen MJ, Cummings JP. Clinical and financial impact of drug-eluting stents: the US academic experience. *J Am Coll Cardiol*. 2005;45(suppl A):73A. Abstract.
20. Greenberg D, Bakhai A, Cohen DJ. Can we afford to eliminate restenosis? Can we afford not to? *J Am Coll Cardiol*. 2004;43:513–518.
21. Cohen DJ, Bakhai A, Shi C, Githiora L, Lavelle T, Berezin RH, Leon MB, Moses JW, Carrozza JP Jr, Zidar JP, Kuntz RE. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial. *Circulation*. 2004;110:508–514.
22. Bowen J, Hopkins R, He Y, Blackhouse G, Lazzam C, Tu J, Cohen E, Tarride J-E, Goeree R. Systematic review and cost-effectiveness analysis of drug eluting stents compared to bare metal stents for percutaneous coronary interventions in Ontario: interim report for the Ontario Ministry of Health and Long-Term Care. Hamilton, Ontario, Canada: Program for Assessment of Technology in Health, McMaster University; December 2005. Report No. HTA002–0512. Contract No. 06129. Available at: http://www.path-hta.ca/DESreport.pdf. Accessed October 4, 2006.
23. Shrive FM, Manns BJ, Galbraith PD, Knudtson ML, Ghali WA. Economic evaluation of sirolimus-eluting stents. *Can Med Assoc J*. 2005;172:345–351.
24. Mittmann N, Brown A, Seung SJ, Coyle D, Cohen E, Brophy J, Title L, Oh P. Economic evaluation of drug eluting stents. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment; February 2005. Technology report No. 53. Available at: https://www.ccohta.ca/publications/pdf/272_drug_eluting_stents_tr_e.pdf. Accessed October 4, 2006.
25. Brophy J, Erickson L. An economic analysis of drug eluting coronary stents: a Quebec perspective. Montreal, Canada: Agence d'evaluation des technologies et des modes d'intervention en sante (AETMIS). Montreal: Canada; September 2004. AETMIS 04-04. Available at: www.aetmis.gouv.qc.ca. Accessed October 4, 2006.
26. Rinfret S, Cohen DJ, Tahami Monfared AA, LeLorier J, Mireault J, Schampaert E. Cost-effectiveness of the sirolimus-eluting stent in high-risk patients in Canada: an analysis from the C-SIRIUS trial. *Am J Cardiovasc Drugs*. 2006;6:159–168.
27. Lord SJ, Howard K, Allen F, Marinovich L, Burgess DC, King R, Atherton JJ. A systematic review and economic analysis of drug-eluting coronary stents available in Australia. *Med J Aust*. 2005;183:464–471.
28. Ward MR. Cost-benefit of drug eluting stents: time for a reality check. *Heart Lung Circ*. 2005;14:74–77.
29. Ekman M, Sjogren I, James S. Cost-effectiveness of the Taxus paclitaxel-eluting stent in the Swedish healthcare system. *Scand Cardiovasc J*. 2006;40:17–24.
30. Kaiser C, Brunner-La Rocca HP, Buser PT, Bonetti PO, Osswald S, Linka A, Bernheim A, Zutter A, Zellweger M, Grize L, Pfisterer ME. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). *Lancet*. 2005;366:921–929.
31. Bagust A, Grayson AD, Palmer ND, Perry RA, Walley T. Cost effectiveness of drug eluting coronary artery stenting in a UK setting: cost-utility study. *Heart*. 2006;92:68–74.
32. Coronary artery stents rapid systematic review and economic evaluation (addendum B). Commissioned by NHS R&D HTA Programme on behalf of the National Institute for Clinical Excellence. Produced by Liverpool Reviews & Implementation Group. Liverpool, UK; 2003. Available at: http://www.nice.org.uk/download.aspx?o=76209. Accessed October 4, 2006.
33. Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. *N Engl J Med*. 2005;353:1516–1522.
34. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
35. Greenberg D, Cohen DJ. Examining the economic impact of restenosis: implications for the cost-effectiveness of an antiproliferative stent. *Z Kardiol*. 2002;91(suppl 3):137–143. Abstract.
36. Greenberg D, Bakhai A, Neil N, Berezin RH, Ho KK, Cutlip DE, Kuntz RE, Cohen DJ. Modeling the impact of patient and lesion characteristics on the cost-effectiveness of drug-eluting stents. *J Am Coll Cardiol*. 2003;41(suppl A):538A. Abstract.
37. Cutlip DE, Chauhan MS, Baim DS, Ho KKL, Popma JJ, Carrozza JP, Cohen DJ, Kuntz RE. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol*. 2002;40:2082–2089.
38. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773–1780.
39. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315–1323.
40. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet*. 2003;362:1093–1099.
41. Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation*. 2003;108:788–794.
42. Eisenberg MJ, Filion KB, Azoulay A, Brox AC, Haider S, Pilote L. Outcomes and costs of coronary artery bypass graft surgery in the United States and Canada. *Arch Intern Med*. 2005;165:1506–1513.
43. Pfisterer ME. Late clinical events related to late stent thrombosis after stopping clopidogrel: prospective randomized comparison between drug-eluting versus bare-metal stenting. Presented at: Late-Breaking Clinical Trials, American College of Cardiology, 55th Annual Scientific Session; March 14, 2006; Atlanta, Ga.
44. Galanaud JP, Delavennat J, Durand-Zaleski I. A break-even price calculation for the use of sirolimus-eluting stents in angioplasty. *Clin Ther*. 2003;25:1007–1016.

45. Oliva G, Espallargues M, Pons JM. Antiproliferative drug-eluting stents: systematic review of the benefits and estimate of economic impact. *Rev Esp Cardiol.* 2004;57:617–628.
46. Marco Valgimigli M, Percoco G, Cicchitelli G, Campo G, Gardini E, Pellegrino L, Malagutti P, Giretti C, Ferrari R. New and old strategies to afford the liberal use of drug-eluting stents in real-life scenarios. *Eur Heart J.* 2005;7(suppl K):K31–K35.
47. Kong DF, Eisenstein EL, Sketch MH Jr, Zidar JP, Ryan TJ, Harrington RA, Newman MF, Smith PK, Mark DB, Califf RM. Economic impact of drug-eluting stents on hospital systems: a disease-state model. *Am Heart J.* 2004;147:449–456.
48. Shrive FM, Ghali WA, Lewis S, Donaldson C, Knudtson ML, Manns BJ. Moving beyond the cost per quality-adjusted life year: modelling the budgetary impact and clinical outcomes associated with the use of sirolimus-eluting stents. *Can J Cardiol.* 2005;21:783–787.
49. Gunn J, Morton AC, Wales C, Newman CMH, Crossman DC, Cumberland DC. Drug eluting stents: maximising benefit and minimising cost. *Heart.* 2003;89:127–131.
50. Tarricone R, Marchetti M, Lamotte M, Annemans L, de Jong P. What reimbursement for coronary revascularization with drug-eluting stents? *Eur J Health Econ.* 2004;5:309–316.
51. Ikeda S, Kobayashi M. Economic evaluation of drug-eluting stents in Japan. *Keio J Med.* 2006;55:15–22.
52. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA.* 2005;293:2126–2130.
53. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet.* 2004;364:1519–1521.
54. Eisenberg MJ. Drug-eluting stents: some bare facts. *Lancet.* 2004;364:1466–1467.

Response to Eisenberg

Jason Ryan, MD, MPH; David J. Cohen, MD, MSc

In this issue of *Circulation*, we and Dr Eisenberg have reviewed the data on the economic impact of drug-eluting stents (DES) and come to seemingly opposite conclusions. In this debate, as in many others, however, the true value lies not in the conclusions themselves but in exploring the reasons for these alternative views. In the case of the DES controversy, 2 fundamental differences largely explain our divergent conclusions. The first is regarding the principle that cost-effectiveness always reflects an incremental analysis. In other words, a device or procedure cannot be evaluated in a vacuum but rather must be compared with an alternative treatment strategy. Taken to its logical conclusion, this concept implies that economic analyses should be focused on specific patient subgroups (based on any number of potential patient characteristics), within the bounds of evidence to distinguish differences in cost and clinical effectiveness. This concept of incremental analysis is the basis for Dr Eisenberg's assertion that conclusions about cost-effectiveness of DES based on clinical trials reflect only the specific population under investigation. We wholeheartedly agree with this point and acknowledge that this is an important limitation of virtually all trial-based economic evaluations. In an ideal world, it would be most efficient to allocate DES specifically to those patients for whom they are most cost-effective and to withhold them from patients who derive only marginal benefit. Unfortunately, at present, the healthcare reimbursement systems in most countries are not sufficiently sophisticated to accommodate this level of analysis. Indeed, decisions about reimbursement for new medical technologies rarely differentiate between populations that derive different levels of absolute benefit (and, as a result, different cost-effectiveness levels). This contrast between optimal resource allocation at the individual level versus at the population level is 1 of the key differences between Dr Eisenberg's view and our own. The second key difference between our position and that of Dr Eisenberg is the perspective of the analysis. Virtually all of the data we cite are based on studies conducted within the United States, whereas most of the analyses cited by Dr Eisenberg are derived from studies conducted in other countries such as Canada and Switzerland. In addition to different care patterns, these countries tend to have lower costs for procedures and hospitalizations and spend far less on health care than in the United States, and these factors would tend to minimize the economic benefit of DES. In the case of the debate on DES versus bare metal stents, differences in the country chosen for the analysis may be at least as important as the underlying patient population. In light of these considerations, we believe that there is more agreement than disagreement in this debate. There is little question that DES are more cost-effective for patients at higher risk of restenosis than for patients for whom the restenosis risk is relatively low. Optimal application of DES technology would certainly focus on those patients for whom it is highly cost-effective. Given the realities of our current reimbursement system, however, it seems unlikely that such fine gradations can be reliably enforced. Therefore, if one accepts the concept that DES should be evaluated in aggregate, we believe that the data are clear. At least from the standpoint of the US healthcare system, the balance of costs and benefits currently favors DES implantation for the overall percutaneous coronary intervention population. Given the numerous differences in practice patterns, treatment costs, and cost-effectiveness thresholds, however, it is clear that this conclusion cannot be readily extrapolated to other countries and healthcare systems and that additional population-based analyses are needed.